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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,432	BUSCHMANN ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 10/17/03. The amendment has been entered. Claims 2, 5, 7-9 and 13-23 have been cancelled. Claims 1, 4 and 12 have been amended. Claims 1, 3, 4, 6 and 10-12 are currently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112

3. Claims 1, 3, 4, 6 and 10-12 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for enhancing arteriogenesis and/or the growth of collateral arteries and/or other arteries from said collateral arteries in mammals, wherein the method comprises delivery of TGF-beta 1 polypeptide directly to the organ or tissue of said mammals where arteriogenesis is desired, does not reasonably provide enablement for the method wherein the TGF-beta 1 is not directly delivered to the organ or tissue where arteriogenesis is desired. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims for the reasons of record.

Response to Arguments

3. Applicant's arguments filed 10/17/03 have been fully considered but they are not persuasive.

4. First, the applicants assert that the claims were rejected under 35 USC 12, first paragraph because the claims encompassed using a TGF-beta1 derivative or functionally equivalent substance. Applicants argue that the claims no longer recite the use of derivatives or functionally equivalent substances; therefore the rejection should be withdrawn.

5. In response, it is acknowledged that the claims no longer recite the use of TGF-beta1 derivatives or functionally equivalent substances. It is also pointed out that the rejection of claims under 35 USC 112, first paragraph for the inadequate written description of TGF-beta1 derivatives and functionally equivalent substances was withdrawn in the previous Office Action. Therefore, the claims are no longer rejected under 35 USC 112, first paragraph for lacking adequate written description.

6. Second, the applicants' traverse the rejection of the instant claims under 35 USC 112, first paragraph for not being fully enabled. Applicants submit that an intravenous, intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration of TGF-beta-1 will deliver TGF-beta-1 to contact the target organ or tissue because as long as the administered TGF-beta-1 is absorbed by the body, which there is no evidence or reason why it would not, there will be TGF-beta-1 contacting the target organ or tissue. Applicants also assert that the administration of TGF-beta-1 by any of the routes recited in claim 1 (even not directly to the collateral arteries) should be effective in contacting the target organ or tissue with TGF-beta-1. For instance, after an intraperitoneal, subcutaneous or intramuscular administration, some of the

TGF-beta-1 (a peptide of 25 kD) molecules will be absorbed into the circulation and be transported to the target organ or tissue. Of course, intravenous administration will no doubt be effective in contacting the target organ or tissue with TGF-beta-1.

In response, it is acknowledged that the TGF-beta-1 need not be delivered directly to the preexisting collateral arteries because the TGF-beta-1 can enhance arteriogenesis from preexisting arteries, not just preexisting collateral arteries. However, the claim still encompasses enhancing arteriogenesis from preexisting arteries (or preexisting collateral arteries) in an organ or tissue of interest by administering TGF-beta-1 by several different routes of administration, including intraperitoneal, subcutaneous and intramuscular administration. Therefore, the claims, as broadly written, encompass the enhancement of arteriogenesis in the brain by administering the TGF-beta-1 intramuscularly (or intraperitoneally, or subcutaneaously). Applicants contend that administering TGF-beta-1 intramuscularly would result in the absorption of TGF-beta-1 into the circulation and transported to the target organ or tissue. However, as indicated in the previous Office Action, there are a number of problems recognized in the art with respect to protein drugs. Specifically, it was indicated that Shire taught,

> "The formulation of protein therapeutics is more difficult than for traditional small-molecule drugs, because of the complex composition and physical properties of the proteins. In particular, the importance of maintaining protein confirmation makes this task especially difficult. **Loss of protein activity or increased immunogenicity** can result without any covalent chemical modifications. Many of the **degradative pathways** in proteins, such as **proteolysis, deamidation, oxidation, or self-association**, will be subject to a diverse set of solution conditions. Generally, especially for a liquid formulation, it is not possible to produce a formulation that will eliminate all of the potential routes of inactivation." See paragraph bridging pages 231-232. (Emphasis Added)

Therefore, it is clear that administering the TGF-beta-1 protein to a site other than the target organ or tissue and relying on absorption of the TGF-beta-1 protein in to the circulation to

deliver the TGF-beta-1 to the target organ/tissue would expose the TGF-beta-1 to degradation as well as a possible immune response before the TGF-beta-1 could reach the target organ/tissue. Furthermore, without a mechanism to direct the TGF-beta-1 specifically to the target organ/tissue, one of skill in the art would not be able to reasonably expect that administering TGF-beta-1 to a site other than the target site would result in enhancement of arteriogenesis at the target organ/tissue without performing an undue amount of additional experimentation. It is noted that there are no working examples in the specification which would indicate that TGF-beta-1 can be administered to a specific organ/tissue by administering the TGF-beta-1 at a site other than the target organ/tissue (e.g., intramuscular, intraperitoneal or subcutaneaous administration).

Additionally, it was indicated in the previous Office Action that Scholz et al. (Angiogenesis Vol. 4; p. 247-257; 2001) indicated the unpredictable nature of arteriogenesis as a therapeutic method for treating vascular diseases. Specifically, it was indicated that Scholz taught,

"Collateral vessels exhibit the same morphology whether they had formed in the heart, limbs or brain or in dogs, rabbits or mouse. They are tortuous because they also increase lengthwise in a restricted space. In animals larger than the mouse, they develop an intima, and initially, many arterioles participate in arteriogenesis, but only a few mature into large arterial channels which, when arterial occlusion had proceeded slowly enough, can replace the occluded artery to a significant proportion. **Therapy with a single growth factor in animals with occluded femoral arteries significantly increased the speed of arteriogenesis but does not significantly increase the level of adaptation. It appears that the master gene for arteriogenesis still awaits discovery**." (See p. 247, abstract). (Emphasis Added).

Therefore, it is unpredictable that protein therapy with a single growth factor could be effectively used to treat vascular disease because the art indicates that although growth factors

can increase the speed of arteriogenesis, they do not necessarily significantly increase the level of adaptation.

Additionally, Kornowski (Circulation 2000) teaches that imprecise localization of therapeutic genes or proteins can be a problem associated with cardiovascular therapy (e.g., see abstract). Specifically, Kornowski teaches, "The primary concern with the pharmacological use of angiogenic growth factors has been potential acceleration of occult neoplastic disease or retinopathy." (See p. 455, bottom of second column).

Therefore, it is clear that there are a number or art recognized problems associated with administering a protein drug intramuscularly, intrapertoneally or subcutaneously in order to induce a desired response at a distant target tissue or organ. The applicants' arguments do not overcome the art-recognized problems; therefore, the rejection is maintained.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by Roberts et al. (PNAS 1986; Vol. 83, p. 4167-4171) for the reasons of record.

Response to Arguments

9. Applicant's arguments filed 10/17/03 have been fully considered but they are not persuasive.

Applicants argue that Roberts does not teach that the administration of TGF-beta-1 results in arteriogenesis, as defined in the specification.

In response, it is first pointed out that Roberts teaches a method comprising the same methods steps of claims 1 and 3. Specifically, Roberts teaches a method wherein TGF-beta polypeptide is administered to newborn mice by subcutaneous injection, resulting in the induction of angiogenesis from preexisting blood vessels and rapid activation of fibroblasts to produce collagen in the area of injection (e.g., see abstract; p. 4167, col. 1; and p. 4168, under "In Vivo Studies").

Regarding the term "angiogenesis" it is respectfully pointed out that Merriam Webster's Collegiate Dictionary, Tenth Ed. Defines angiogenesis as, "the formation and differentiation of blood vessels." (See p. 44). Therefore, the term "angiogenesis" encompasses the formation of any type of blood vessel, including arteries. Although Roberts does not explicitly indicate if the method results in the formation of collateral arteries or other arteries from preexisting arteriolar connections, the fact that Roberts teaches that the method results in induction of angiogenesis indicates that the method results in the formation of blood vessels.

Furthermore, the method of Roberts appears to be identical to the claimed method. Identical methods inherently have identical results. Although Roberts does not explicitly indicate that administration of TGF-beta results in enhanced arteriogenesis and/or the growth of collateral arteries and/or other arteries from preexisting arteriolar connections, the method steps taught by Roberts are identical to the claimed method steps. Therefore, the method of Roberts would inherently have the same results as the claimed method, thus the instant claims are anticipated by the teaching of Roberts.

Regarding applicants' arguments that the limitations of 10-12 were not considered, it is acknowledged that claims 10-12 are not anticipated by Roberts, in view of the limitations of claims 10-12. Therefore, the rejection of claims 10-12 under 35 USC 102(b) are withdrawn.

Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. Claims 1, 4 and 6 remain rejected and claim 12 is now rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. (PNAS 1986; Vol. 83, p. 4167-4171) in further view of Asahara (Circulation, 1995, Vol 92 (9, Suppl.) pages II365-371).

Claim 1 is rejected based on the teaching of Roberts for the reasons set forth above.

Roberts teaches a method of inducing angiogenesis by administering a TGF-beta polypeptide to a mammalian subject, as mentioned above.

Roberts does not teach that the method further comprises contacting the organ/tissue with a growth factor or cytokine (claim 4); wherein said growth factor or cytokine is b-FGF, PDGF, TNF-alpha, IL-1, IL-6 or VEGF (claim 6), or that the agent is administered to a subject after surgical treatment that damages or destroys arteries.

However, Asahara teaches a method for inducing angiogenesis by administering a combination of two angiogenic molecules: b-FGF and VEGF to rabbits ten days after surgical induction of unilateral hind limb ischemia (e.g., see abstract). Asahara teaches that the

combination treatment of b-FGF and VEGF has a synergistic effect on angiogenesis in vivo. Specifically, Asahara teaches,

> "Combined administration of VEGF and bFGF stimulates significantly greater and more rapid augmentation of collateral circulation, resulting in superior hemodynamic improvement compared with either VEGF or bFGF alone. This synergism of two angiogenic mitogens with different target cell specificities may have important implications for the treatment of severe arterial insufficiency in patients whose disease is not amenable to direct revascularization." (See Abstract)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of inducing angiogenesis using TGF-beta taught by Roberts such that the method comprised administration of TGF-beta and VEGF or b-FGF to a mammal after surgical treatment that damages or destroys arteries, with a reasonable expectation for success.

The motivation to modify the method taught by Roberts is provided by Asahara, who indicates that combinations of angiogenic mitogens may have important implications for the treatment of sever arterial insufficiency in patients whose disease is not amenable to direct revascularization.

Response to Arguments

12. Applicant's arguments filed 10/17/03 have been fully considered but they are not persuasive.

Applicants argue,

> "There would have been no motivation to modify the method of Roberts et al. because the method of Roberts et al. was aimed merely at validating a hypothesis that TGF-beta is an important mediator of tissue repair (see the last sentence of the Abstract of Roberts et a1.). Roberts et al. did not concern with the treatment of severe arterial insufficiency. A person of ordinary skill in the art would have no desirable reason of adding VEGF or bFGF to the method of Roberts et al. because the person would have known that the

> VEGF or bFGF would very likely complicate the picture so that the person would not know whether a certain biological effect was caused by TGF-beta or the other growth factor added. The person also would not have been motivated to administer VEGF or bFGF along with TFG-beta in the method of Roberts et al. because adding VEGF or bFGF would not help to validate the hypothesis that TGF-beta is an important mediator of tissue repair." (See pages 8-9 of the response).

13. In response, it is respectfully pointed out that it is irrelevant what the aim of the Roberts study was, the fact the results indicate that the method of administering TGF-beta enhances angiogenesis in an animal is sufficient information to one of ordinary skill to combine the method of Roberts with the teaching of Asahara to create a method comprising administering TGF-beta and another growth factor (specifically, VEGF or b-FGF) in order to enhance angiogenesis (which would encompass arteriogenesis considering Webster's definition of angiogenesis) in an animal. It is irrelevant that Roberts did not concern with the treatment of severe arterial insufficiency. Furthermore, in response to applicant's argument that the person would not have been motivated to administer VEGF or bFGF along with TFG-beta in the method of Roberts et al. because adding VEGF or bFGF would not help to validate the hypothesis that TGF-beta is an important mediator of tissue repair, it is respectfully pointed out that one of ordinary skill would recognize that Roberts teaches a method of enhancing angiogenesis by administering TGF-beta and one of ordinary skill in the art would also recognize that Asahara teaches a different method for enhancing angiogenesis comprising administering a combination of growth factors (VEGF and b-FGF). Therefore, one of ordinary skill in the art would have recognized that the methods of Roberts and Asahara could be combined into a new method for enhancing angiogenesis comprising administering a combination of growth factors including TGF-beta and VEGF or b-FGF with a reasonable expectation of success.

For instance, one of ordinary skill in the art would recognize that Roberts et al. teaches a method comprising administering TGF-beta to an animal. Roberts also indicates that administering TGF-beta to the animal resulted in angiogenesis. Considering that Webster's dictionary defines angiogenesis as "the formation and differentiation of blood vessels" (See above, and the previous Office Action) one of ordinary skill would recognize that the term "angiogenesis" would encompass the formation of any type of blood vessel, including arteries. Therefore, one of ordinary skill would recognize that Roberts et al. teaches a method of inducing angiogenesis in an animal by administering TGF-beta to the animal. One of ordinary skill in the art would also recognize that Asahara teaches a method of inducing angiogenesis in an animal by administering a combination of growth factors, specifically b-FGF and VEGF, wherein a combination of the two growth factors results in an effect that is greater than the effect of either growth factor alone. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method of Roberts et al. such that the method comprised further administering another growth factor, such as VEGF or b-FGF, in order to enhance angiogenesis (which as defined by Webster's Dictionary encompasses arteriogenesis) with a reasonable expectation of success. As previously indicated, the motivation is provided by Asahara who indicates that using combinations of growth factors can have a greater than additive effect on angiogenesis.

Therefore, applicants' arguments are not persuasive and the rejection is not withdrawn.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10.

11. Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. (PNAS 1986; Vol. 83, p. 4167-4171) in further view US Patent 5,482,851(Derynck et al.).

12. The instant claims are drawn to a method comprising administering TGF-beta-1 to a subject (claim 1), wherein the TGF-beta-1 is recombinant TGF-beta-1 (claim 2).

13. It is noted that claim 1 is taught by Roberts, as indicated above (in the 102(b) rejection). However, upon further consideration, Roberts teaches that the TGF-beta that is administered is purified from human platelets (see p. 4167, second column). Therefore, Roberts does not explicitly teach that the TGF-beta used is recombinant TGF-beta.

14. However, Derynck teaches recombinant TGF-beta and methods of making and purifying recombinant human TGF-beta (e.g., see abstract).

15. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Roberts such that recombinant human TGF-beta (as taught by Derynck) is used instead of non-recombinant TGF-beta, with a reasonable expectation of success.

16. The motivation to use recombinant human TGF-beta is provided by Derynck, which teaches,

> "TGF-beta prepared by purification from biological materials present a risk of contamination by infectious agents such as HTLV-III or hepatitis viruses. Accordingly, it is an object of this invention to prepare TGF-beta from sources that do not present a risk of contamination."

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. (PNAS 1986; Vol. 83, p. 4167-4171) in further view US Patent 6,121,246 (Isner).

20. The instant claims are drawn to a method comprising administering TGF-beta-1 to a subject (claim 1), wherein said method is applied to a subject suffering from a vascular disease or a cardiac infarct or a stroke (claim 10), wherein said vascular disease is arteriosclerosis and/or a hyperlipidemic condition, **a coronary artery disease**, cerebral occlusive disease, peripheral occlusive disease, visceral occlusive disease, **renal artery disease**, mesenterial arterial insufficiency or an ophthalmic or retinal occlusion (claim 11). (Emphasis added).

It is noted that claim 1 is taught by Roberts, as indicated above (in the 102(b) rejection).

Roberts does not teach that the TGF-beta is administered to a subject suffering from a vascular disease or a cardiac infarct or a stroke such as the renal artery disease like renal ischemia.

However, Isner teaches a method of treating ischemia in a subject by administering a nucleic acid encoding TGF-beta directly to the site of ischemia, wherein the ischemia can be cardiovascular ischemia and/or renal ischemia (e.g., see abstract or column 2, lines 54-61).

Therefore, it would have been prima facie obvious to one of skill in the art at the time the invention was made to modify the method taught by Isner such that TGF-beta polypeptide is administered directly to the site of ischemia with a reasonable expectation of success.

It is noted that Isner teaches administrating a nucleic acid encoding TGF-beta. One of ordinary skill in the art would recognize that a method comprising administering a nucleic acid

encoding TGF-beta must result in the expression of the TGF-beta polypeptide in order to work. That is, it would be readily recognized to an ordinary artisan that the functional element of the gene therapy method is the expression of the TGF-beta polypeptide. Therefore, one of ordinary skill would recognize that administering either a nuclei acid encoding TGF-beta or the TGF-beta polypeptide itself could be used to treat ischemia in a mammal and the motivation to use the TGF-beat polypeptide rather than a nuclei acid encoding TGF-beta would be a matter of experimental preference.

Conclusion

No claim is allowed.

14. THIS ACTION IS MADE NON-FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this ~~final~~ non-final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
Art Unit 1635